STUDY OF SYNTHETIC APPROACHES OF SOME 1,3,4-TRISUBSTITUTED PYRAZOLE DERIVATIVES

# SYNOPSIS

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By

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# SYNOPSIS

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**1. Title:** STUDY OF SYNTHETIC APPROACHES OF SOME 1,3,4-TRISUBSTITUTED PYRAZOLE DERIVATIVES

## 2. Introduction

The development of new synthetic approaches of various heterocyclic compounds has always been a key research area in the field of organic chemistry (Eicher et al. 2013; Katritzky et al. 2010). The various types of heterocyclic compounds have been given in figure **1**.

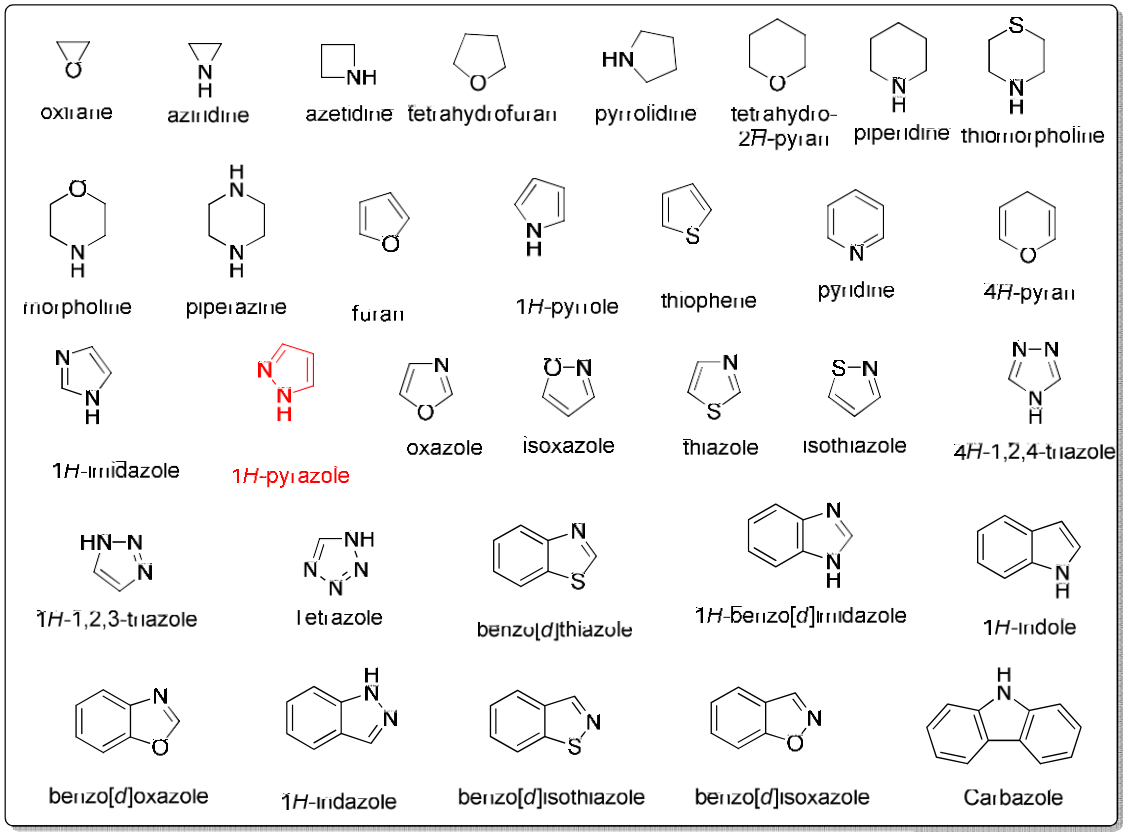



**Figure 1.** Various types of heterocyclic compounds

Amongst heterocycles, the pyrazole holds a significant position due to the presence in various natural and synthetic products which exhibit a wide range of biological activities (Jamwal et al. 2013). The pyrazole, an important heterocyclic building block (Elguero et al. 2002), is the core constituent of several agrochemicals (Lamberth 2007) and polymers (Danel et al. 1999; Navarro & Lippert 2001) as shown in figure **2**.

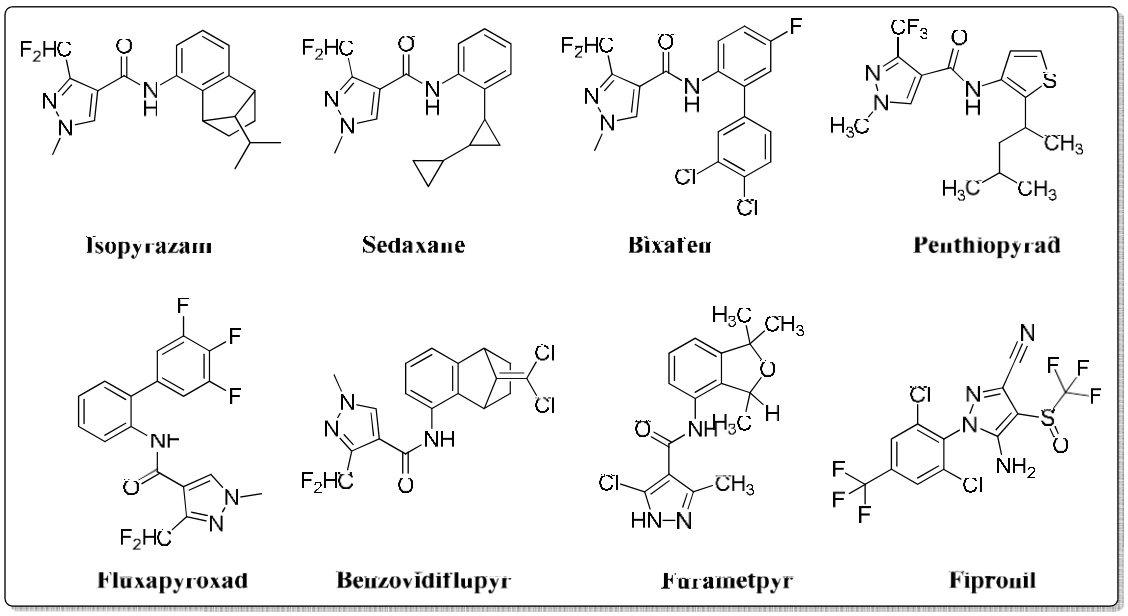



**Figure 2.** The pyrazole derivatives used as Fungicides/Insecticides

The pyrazole derivatives including celecoxib, fipronil, lonazolac, tolpiprazole, crizotinib, ruxolititnib, Viagra and so many (Figure **3**) possess a broad spectrum of biological activities such as antibacterial, anti-inflammatory, antidepressant, antitumor and anti hyperglycemic activities (Dömling & Ugi 2000; Elguero et al. 2002; Kappe 2000; Penning et al. 1997; Singh et al. 2004; Strecker 1850; Terrett et al. 1996).

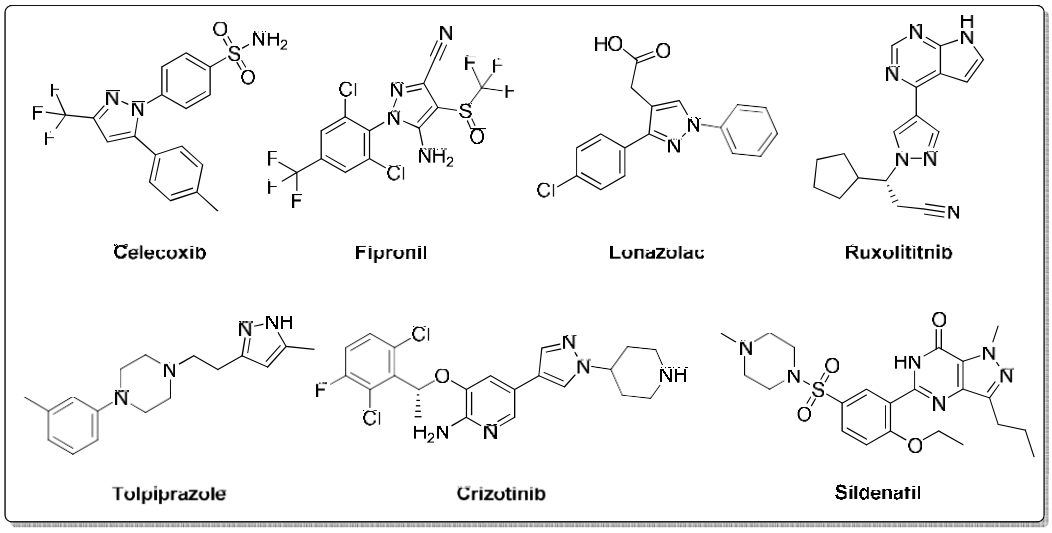



**Figure 3.** Pyrazole derivatives as commercial drug candidates

Several reports have been found in the literature regarding the synthesis of 1,3,4-trisubstituted pyrazole derivatives exhibiting significant biological activities (Wang et al. 2015). Pyrazoles such as N-aryl pyrazoles are the vital scaffolds exhibiting widespread utilization in pharmaceutical as well as in agrochemical industries (Fan & Katritzky 1996; Kost & Grandberg 1966) and various synthetic approaches have been reported well in the literature (Babinski et al. 2011; Grotjahn et al. 2002; Hari et al. 2007; Jackowski et al. 2011; Ma et al. 2011; Martín et al. 2006). The most commonly synthetic approaches of the pyrazoles reported in the literature are:

i. The Knorr synthesis involving condensation of 1,3-dicarbonyls or their equivalents with hydrazines/substituted hydrazines (Calle et al. 2006; Heller & Natarajan 2006; Knorr & Laubmann 1888)
ii. The Pechmann synthesis involving the [3+2] cycloaddition of diazo compounds with alkynes (Faria et al. 2017; v. Pechmann 1898)
iii. The transition-metal-catalyzed C-C or C-N cross coupling on pre-formed pyrazoles (Jiang & Li 2004; Wang et al. 2015)
iv. Copper(II)-catalyzed oxidative N-N bond formation using enamines and nitriles (Neumann et al. 2010; Suri et al. 2012)
v. [4+1] cyclization from $\alpha$-(1,3-dithian-2-yl)enamine ketones and primary amines (Wang et al. 2015)

Regarding substituted pyrazoles, the pyrazoles possessing various functionality at 4-position of the ring received considerable attention since these pyrazoles constitutes the core scaffold of various biologically active heterocyclic compounds (Khloya et al. 2013; Sharma et al. 2011a; Sharma et al. 2010; Sharma et al. 2002; Sharma et al. 2011b). The rigorous literature search revealed that 4-functional pyrazoles have been used as a core scaffold for the synthesis of several heterocyclyl-pyrazole derivatives (Bala et al. 2019).

Owing the importance of pyrazole derivatives we thought worthwhile to study the synthesis of 1,3,4-trisubstituted pyrazoles and set the following objectives:

i. Synthesis of some 4-Cyanopyrazoles and their study with Grignard reagents.
ii. Synthesis of Novel Pyrazolyl Sulfones.
iii. Synthesis of some 4-formylpyrazoles and their applications in the synthesis of various heterocyclic compounds.
iv. Study of OPC-VH reagent in the synthesis of 1,3,4-trisubstituted pyrazoles.
v. Biological evaluation of selected compounds.

## 3. Expected new knowledge

As per review of literature, the synthesis and various biological activities of 1,3,4-trisubstituted pyrazoles are well documented which gives us a chance to investigate the synthesis of various important 1,3,4-trisubstituted pyrazoles using various approaches. Therefore, our studies are focused towards the synthesis, isolation and characterization of 1,3,4-trisubstituted pyrazoles and used them for their biological evaluation. It is expected that the synthesis of 1,3,4-trisubstituted pyrazoles will impart a great role to extend the importance of pyrazoles in the biological fields and it will increase our basic knowledge regarding synthesis, isolation, purification techniques as well as applications of characterization techniques used to characterize novel organic compounds.

## 4. Review of Literature

The literature review revealed that 4-functional pyrazoles have been frequently used as building blocks for the synthesis of 1,3,4-trisubstituted pyrazole derivatives. Some of them are mentioned here.

Bala et al. (2019) reported 4-formylpyrazoles as useful building blocks in synthesis of large variety of organic compounds and heterocycles such as Schiff bases, pyrazolylpyrazolines, pyrazoloquinolinones, 4H-pyrazolopyran, pyrazolylbenzoxazole,

pyrazolothiadiazepines, pyrazolyloxazolone, pyrazolyloxadiazolines, pyrazolylthiadiazolines, imidazolylpyrazoles, pyrazolopyridines, chromenopyrazolones, thiopyranothiazolylpyrazoles and many others which showed excellent biological activities (Figure **4**).

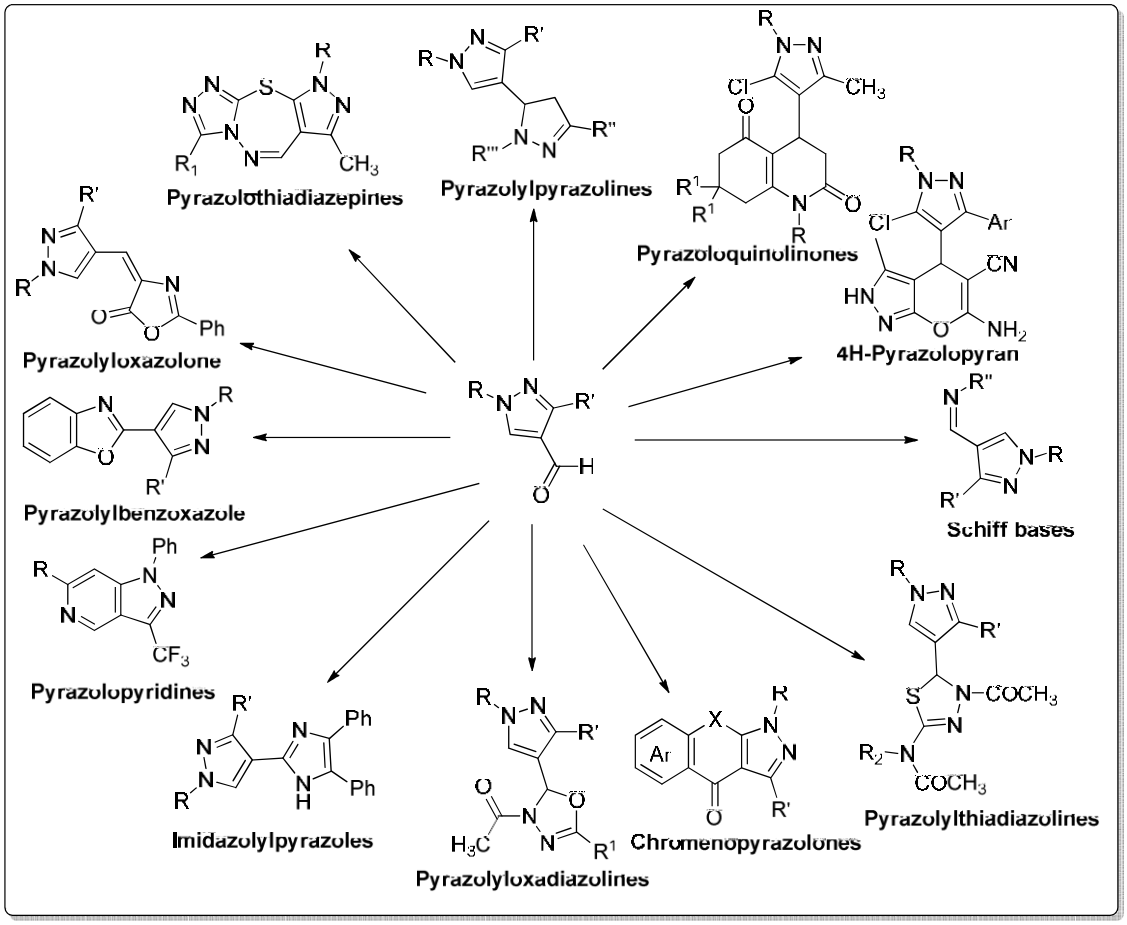
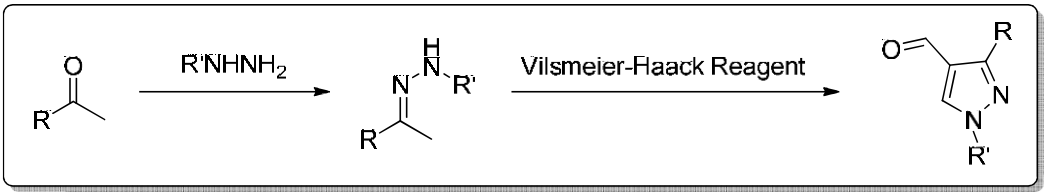



**Figure 4.** Applications of formylpyrazoles

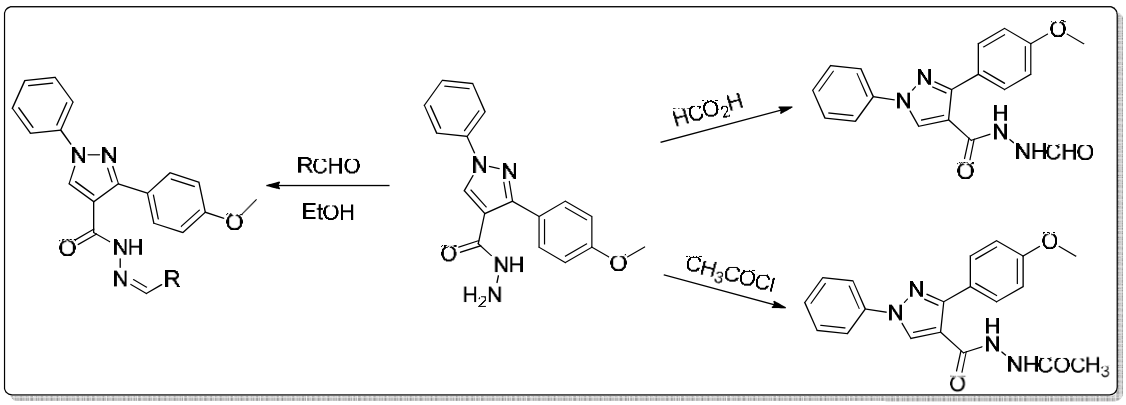
The most common method for the synthesis of 4-formylpyrazoles is the Vilsmeier-Hacck reaction on hydrazones obtained from various acetophenones and hydrazines (Scheme **1**) (Bala et al. 2018; De Luca et al. 2004; Sharma et al. 2002; Singh et al. 2005).



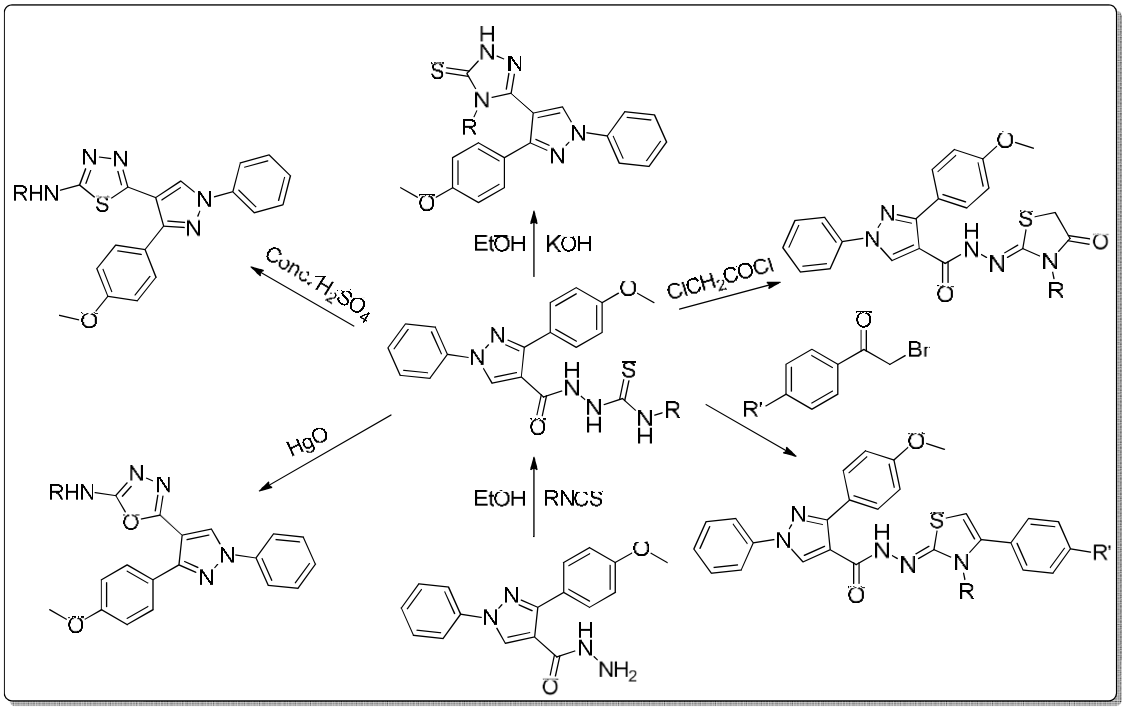

**Scheme 1.**

Bekhit et al. (2019) reported the synthesis of novel 1,3,4-trisubstituted pyrazole derivatives according to the steps outlined in Scheme **2** and Scheme **3**. The synthesized compounds were evaluated for their antiplasmodial activity against *P. berghei* and also

screened for their in vitro antimalarial activity against the chloroquine resistant strain *P. falciparum*, (RKL9).

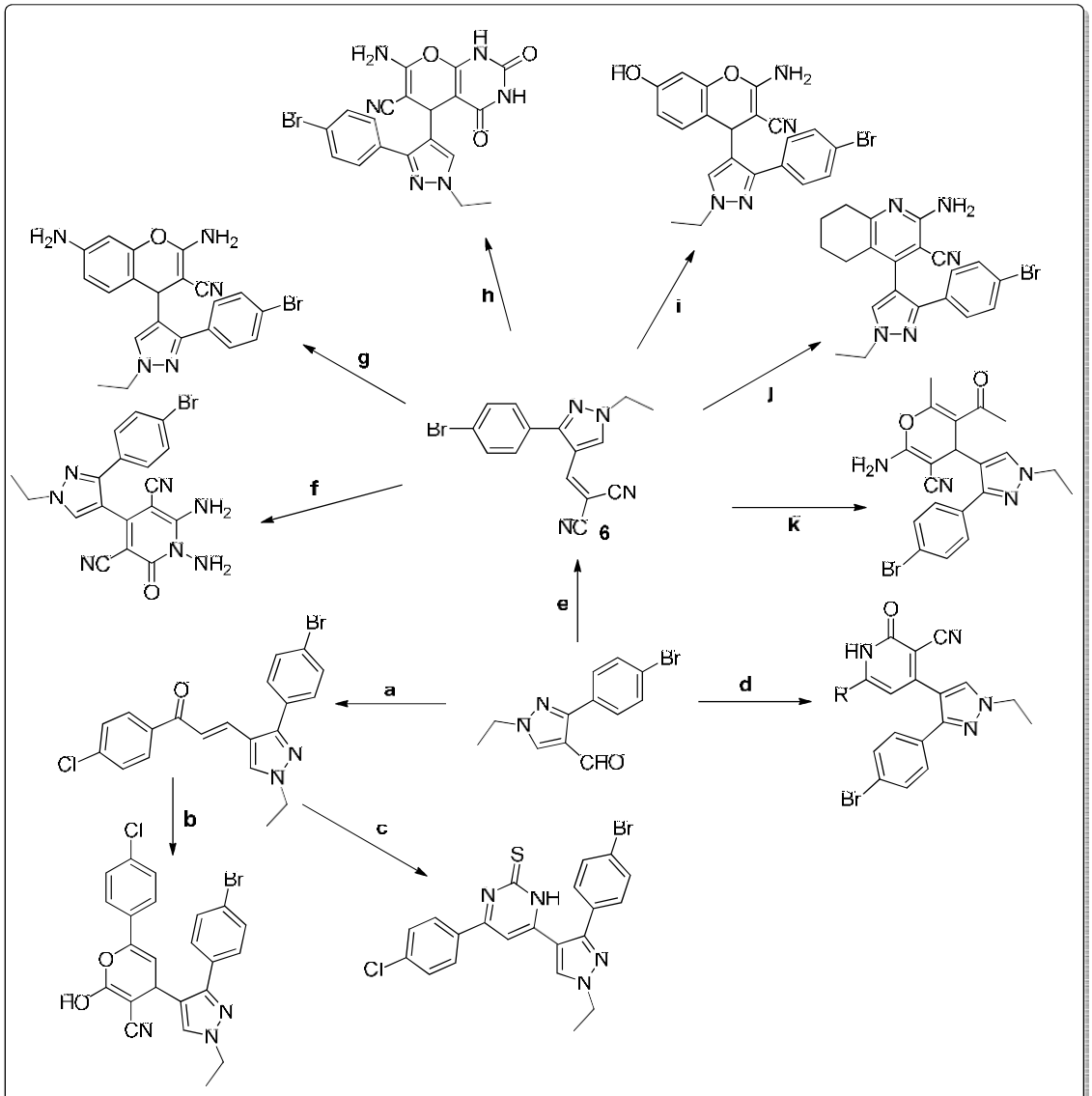



**Scheme 2.**




**Scheme 3.**

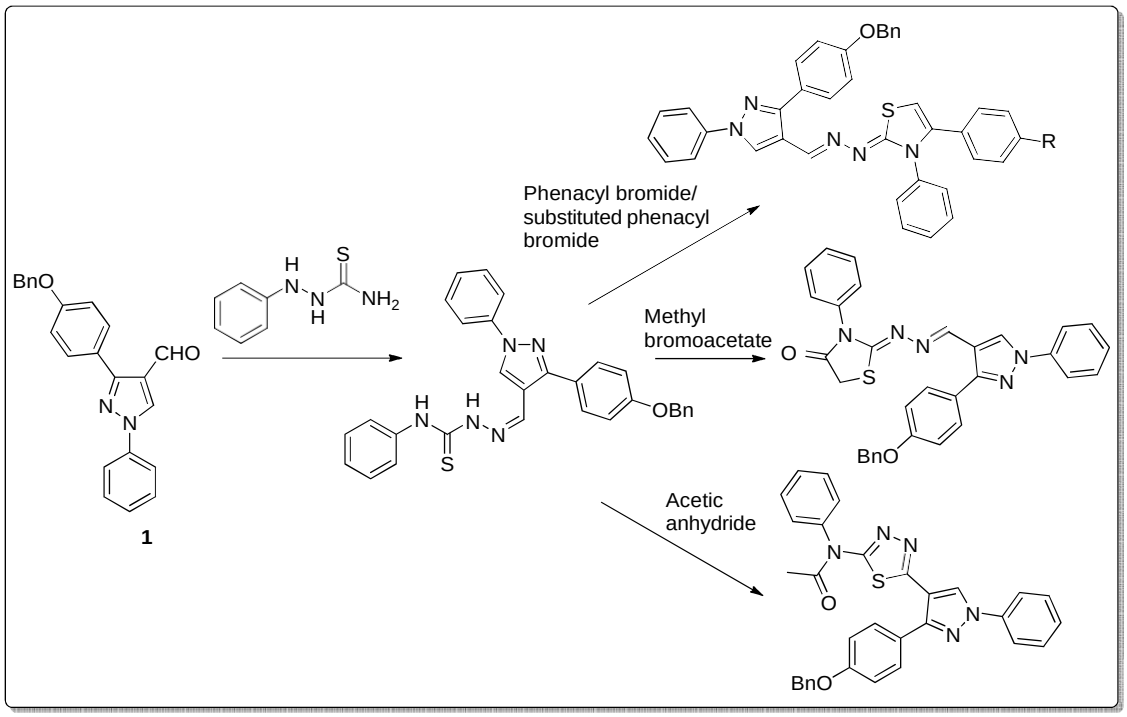
Srour et al. (2018) reported the synthesis of new derivatives of 1,3,4-trisubstituted pyrazole *via* different routes starting with the chalcone (*E*)-3-[3-(4-bromophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-1-(4-chlorophenyl)prop-2-en-1-one and dicarbonitrile 2-[[3-(4-bromophenyl)- 1-ethyl-1*H*-pyrazol-4-yl]methylene]malononitrile derived from 3-(4-bromophenyl)-1*H*- pyrazole-4-carbaldehyde (scheme **4**), and the *in-vitro* evaluation results of anti-cancer activity against various human cancer cell lines.



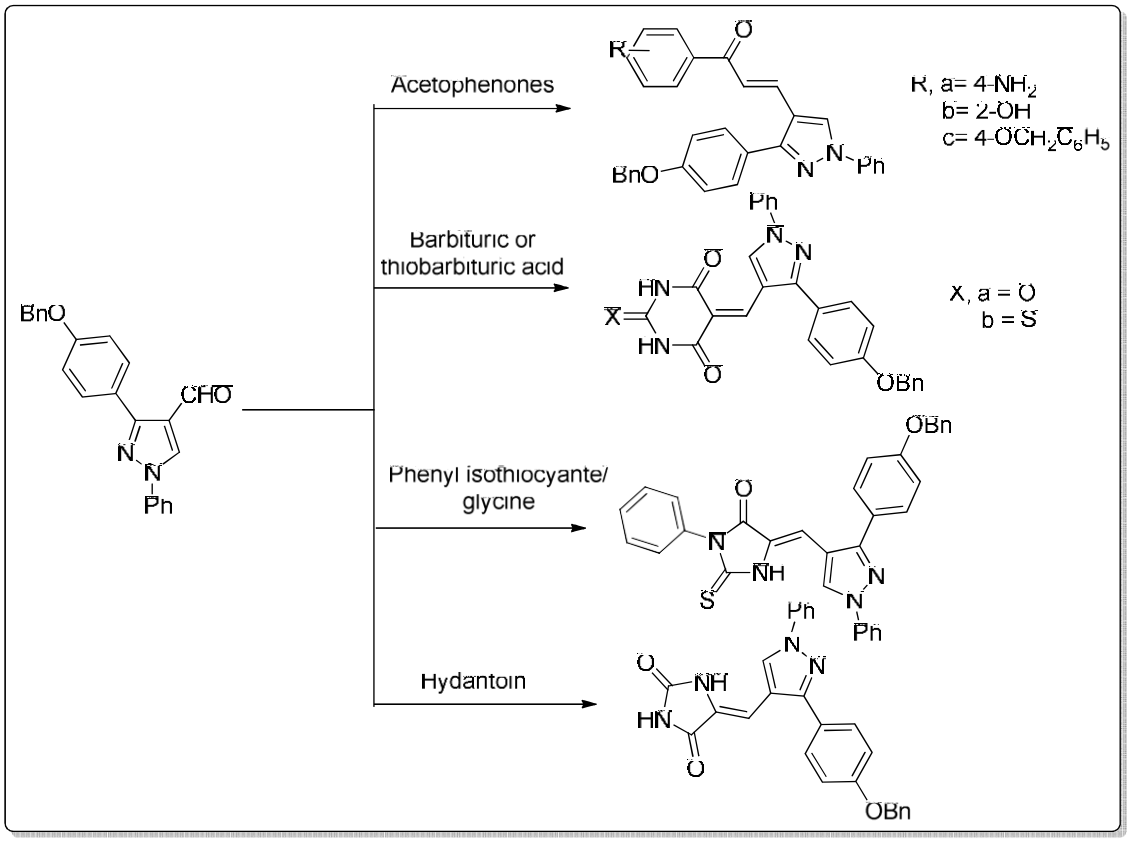
**Reagents and conditions:** (a) 4-Chloroacetophenone, EtONa, stirring, rt; (b) ethyl cyanoacetate, NaOH/EtOH/reflux, 5 h; (c) thiourea, NaOH/EtOH/reflux, 8 h; (d) ethyl cyanoacetate, 2-acetyl aryl derivatives, $NH_4OAc$, EtOH/reflux, 12 h; (e) malononitrile, TEA, EtOH/stirring, rt; (f) cyano acetic acid hydrazide, TEA, EtOH/stirring, rt; (g) 3-aminophenol, TEA, EtOH/stirring, rt; (h) barbituric acid, TEA, EtOH/reflux, 8 h; (i) resorcinol, TEA, EtOH/reflux, 12 h; (j) cyclohexanone, $NH_4OAc$, EtOH/reflux, 8 h; (k) acetylacetone, TEA, EtOH/reflux, 12 h

**Scheme 4.**

Harras & Sabour (2018) reported the synthesis and cytotoxic activity of a series of novel 1,3,4-trisubstituted pyrazole derivatives against three different cancer cell lines namely HCT116, UO-31 and HepG2. The target compounds were synthesized according to the steps outlined in Schemes **5** and **6**.

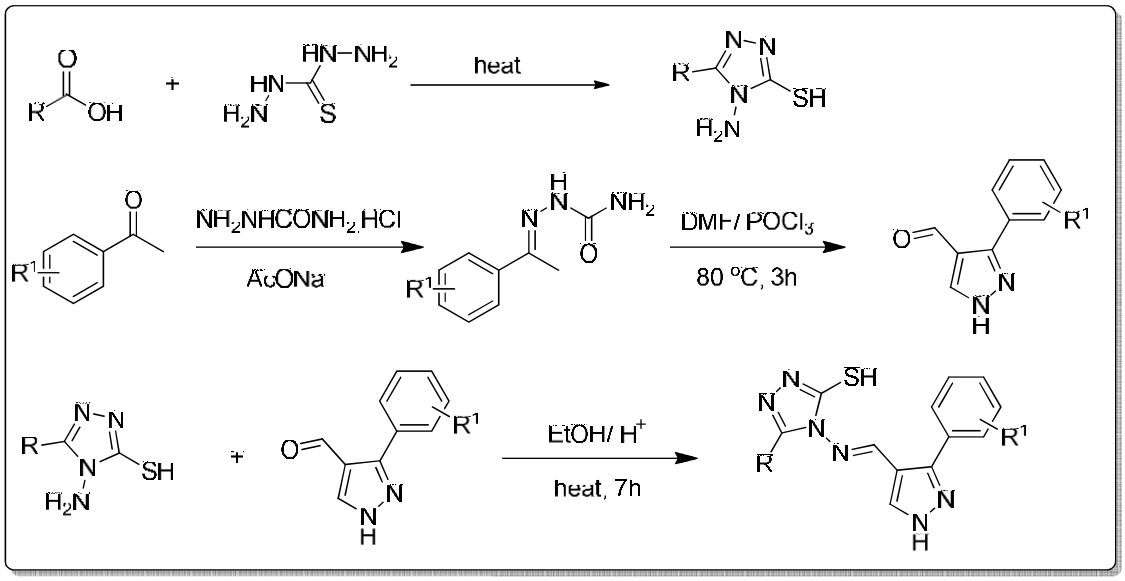



**Scheme 5.**



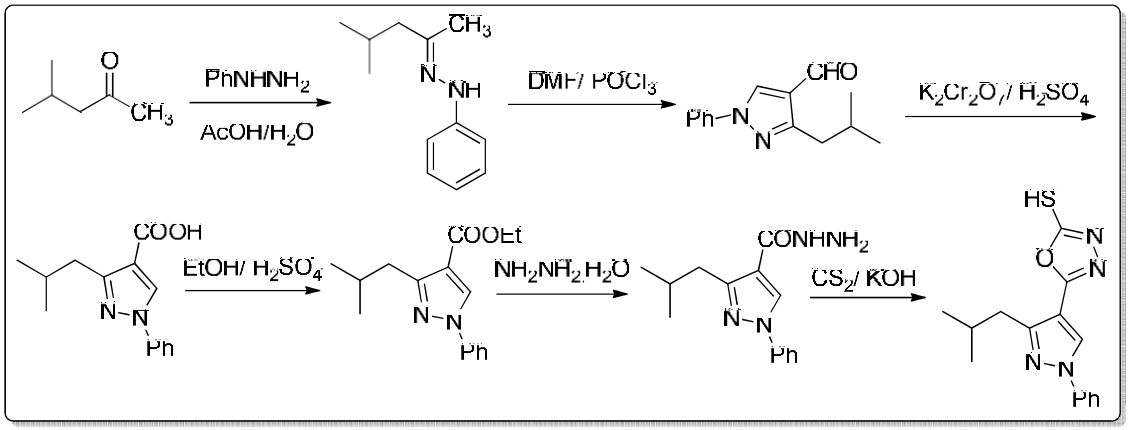

**Scheme 6.**

Malladi et al. (2013) reported the synthesis of Schiff bases which were prepared by the condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol with several 3-substituted pyrazole-4-carboxaldehydes in the presence of concentrated sulphuric acid in ethanol-dioxane mixture as given in Scheme **7**.




**Scheme 7.**

Abu-Zaied et al. (2011) reported the formation of 3-isobutyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde *via* condensation between methyl iso-butyl ketone and phenylhydrazine followed by application of Vilsmeier-Haack reaction. 3-Isobutyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde was converted to 1,3,4-trisubstituted pyrazole derivative by following the steps given in scheme **8**.




**Scheme 8.**

**5. Technical programme**

i. **Name of the experiment:** Study of synthetic approaches of some 1,3,4-trisubstituted pyrazole derivatives

ii. **Location of study:** Lingaya's Vidyapeeth

**iii. Methodology:**

a) Source of Literature

Chemical abstracts, Indian Journal of Chemistry, Indian Journal of Organic Chemistry, Asian Journal of Chemistry, Tetrahedron Letters, Tetrahedron, Journal of Indian Chemical Society, Journal of Australian Chemical Society, Organic Letters, Peragoman Press and Journal of American Chemical Society etc.

b) Pre-laboratory work

The chemicals & reagents required for the synthesis and evaluation of the proposed compounds will be procured from reputed suppliers like Merck, Ranbaxy, Qualigens, Finar etc.

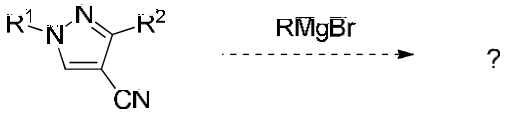
c) Laboratory work

**Step 1: Synthesis**

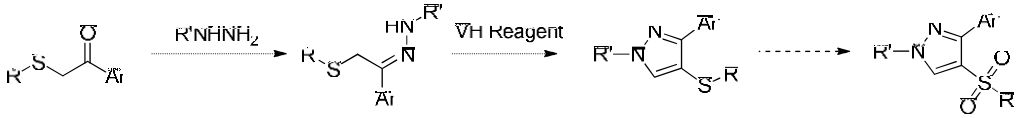
Conventional methods of synthesis will be attempted. The completion of the reaction will be determined by TLC. Advantages and feasibility of the methods will be analyzed.

**Plan of Work:**

i. Synthesis of some 4-Cyanopyrazoles and their study with Grignard reagents.

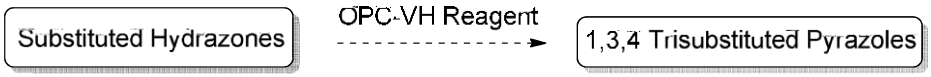



ii. Synthesis of Synthesis of Novel Pyrazolyl Sulfones.




iii. Synthesis of some 4-formylpyrazoles and their applications in the synthesis of various heterocyclic compounds.

iv. Study of OPC-VH reagent in the synthesis of 1,3,4-trisubstituted pyrazoles.




v. Biological evaluation of selected compounds.

**Step 2: Purification**

The synthesized compounds will be purified by different methods like fractional crystallization, recrystallisation, distillation and chromatographic methods. The purity will be ascertained by TLC.

**Step 3: Characterization**

The synthesized compounds will be characterized by:

- Chemical tests for important functional groups.
- With various spectroscopic methods like IR, $^{1}$H NMR, MS/LCMS etc.

**Observation to be recorded**

- State of the compound (solid/liquid)
- If solid, colour of the compound
- Melting point if the compound is solid
- Yield of each compound

  Need to record and interpretation of IR, $^{1}$H NMR, MS/LCMS and other spectra as per requirements to characterize the desired compound.

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